REMARKS

I. Status of the Claims

Claim 2 was cancelled previously. Claims 1 and 3-30 are pending, with claims 12-16 and 26-30 withdrawn from consideration as being directed to non-elected subject matter. Claims 1, 3-11, and 17-25 are under consideration.

II. Previous Rejections

Applicants thank the Examiner for withdrawing the double patenting rejection of claims 1-11 and 17-25. See Office Action, page 2.

III. Rejection under 35 U.S.C. § 103(a)

Claims 1, 3-11 and 17-25 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,536,469 to Jonsson et al. ("*Jonsson*") in view of Breborowicz et al., "Replacement of Glucose with N-Acetylglucosamine in Peritoneal Dialysis Fluid - Experimental Study in Rats," *Peritoneal Dialysius International*, 21(Supplement 3): S365-S367 (2001) ("*Breborowicz*"). Office Action at pages 2-5.

According to the Office, *Jonsson* discloses a sterile medical solution containing glucose or glucose-like compounds for peritoneal dialysis. *Id.* at page 4. The Office acknowledges, however, that *Jonsson* neither discloses "a medical solution containing one or more acetylated or deacetylated amino sugars" nor "the preparation of a final medical solution wherein the pH is 7.4." *Id.* at page 3. A solution comprising one or more acetylated or deacetylated amino sugars is a limitation shared by all claims under consideration, while a finally prepared medical solution wherein the pH is 7.4 is a limitation of claim 23.

The Office contends that *Breborowicz* makes up for these deficiencies of *Jonsson* by "teach[ing] partial replacement of glucose with N-acetylglucosamine (NAG) in peritoneal dialysis fluid results in advantageous preservation of the peritoneal membrane." *Id.* The Office concludes that "[o]ne of ordinary skill in the art would be motivated to combine *Jonsson* et al. in view of *Breborowicz* et al. because *Breborowicz* teaches it is advantageous to partially replace glucose with N-acetylglucosamine (NAG)." *Id.* at page 4. The Office further concludes that "[o]ne of ordinary skill in the art would be motivated to optimize the final medical solution wherein pH is 7.4 because *Jonsson* et al. teaches the final peritoneal dialysis solution optimized at a pH between 6.5 and 7.5." *Id.*

In response to Applicants' arguments presented in the amendment filed on July 13, 2009, the Office argues that entry no. 4466 for glucosamine in the Merck Index, 12th ed. (1996) shows that "N-acetylglucosamine has a melting point of 205 °C with no indication of decomposition" and that based on this information one of ordinary skill in the art would have had a reasonable expectation of success in combining *Jonsson* in view of *Breborowicz*. *Id.* at page 5.

Applicants respectfully disagree and traverse this rejection for the following reasons.

A. A melting point value for N-acetylglucosamine has no bearing on the *thermochemical* stability of N-acetylglucosamine in a solution with a pH of 2.5-3.5

The melting point of a compound is a physical property. It represents the temperature at which the solid form of the compound changes to the liquid form, or at which liquid and solid forms coexist in an equilibrium. The melting point provides no

indication, however, about the stability of the compound *in solution*. Furthermore, the melting point provides no indication about whether the dissolved compound is *stable under specific chemical conditions*, such as, for example, a low pH. Finally, the melting point provides no indication whether the *dissolved compound* is *stable at high temperatures*, which can affect reaction rates.

A compound may chemically decompose in solution under various conditions independently of whether the compound decomposes during the measurement of its melting point. Decomposition is a chemical reaction in which a compound is broken down into simpler compounds or elements, and this reaction can be influenced by factors such as heat or the pH of the solvent.

The entry no. 4466 for glucosamine in the Merck Index, does not provide information regarding the behavior of N-acetylglucosamine in solution, including its chemical stability under low pH conditions or its thermal stability *in solution* at temperatures used for heat sterilization. Nor can such information be deduced from the provided melting point, as explained above. Thus, contrary to the Office's assertion, entry no. 4466 for glucosamine in the Merck Index, does not support any conclusions regarding the behavior of NAG under the conditions recited in the claims, namely being dissolved in a solution with an acidic pH of 2.5-3.5 and being subjected to terminal sterilization.

Furthermore, the instant specification discloses that NAG in fact decomposes when terminally sterilized in conventional medical solutions:

> It has now been found that also amino sugars, e.g. NAG, in conventional medical solutions exhibit an increased cytotoxicity after heat sterilisation. This cytotoxicity depends

> on the formation of toxic degradation products from said amino sugars.

Specification at page 3, lines 32-36 (emphasis added).

Consequently, entry no. 4466 for glucosamine in the Merck Index does not support the Office's assertion that one of ordinary skill in the art would have had a reasonable expectation of success in combining *Jonsson* in view of *Breborowicz*. Thus, for at least this reason, Applicants request that the Office reconsider Applicants' arguments and withdraw this rejection.

B. The Office has failed to make a *prima facie* case of obviousness because it has failed to show that one of ordinary skill in the art would have combined the references as proposed

The law provides that the Office must first make several basic factual inquiries to determine whether the claims of a patent application are obvious under 35 U.S.C. § 103. These factual inquiries, set forth in *Graham v. John Deere*, require the Office to:

> (1) Determine the scope and content of the prior art;
>
> (2) Ascertain the differences between the prior art and the claims in issue;
>
> (3) Resolve the level of ordinary skill in the pertinent art; and
>
> (4) Evaluate evidence of secondary considerations.

See Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). The Office must then evaluate the obviousness or non-obviousness of the claimed invention in view of the results of these inquiries. *Id.*; *see also KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1734 (2007).

Based on the Supreme Court's decision in *KSR*, the Office has announced seven exemplary rationales that may support a conclusion of obviousness. *See* M.P.E.P.

§ 2143. According to these rationales, a conclusion of obviousness based on the combination of prior art reference teachings requires that a person of ordinary skill in the art, without knowing anything of the claimed invention, would have had a good reason or motivation to pursue the combination and would have achieved anticipated success or at least had a reasonable expectation of success in arriving at the claimed invention. If any of these findings cannot be made, then a conclusion of obviousness is not warranted. This is reflected in the published Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR*, for example as follows:

> The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under
> § 103." If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Fed. Reg., Vol. 72, No.195, at 57532 (reference omitted; emphasis added). The guidelines further explain that:

> The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Id. at 57534 (reference omitted; emphasis added).

Furthermore, the Supreme Court in *KSR* confirmed the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a

successful means of combining them is more likely to be non-obvious. *KSR* at 1739-1741. Thus, if the prior art warns against using a certain condition or procedure in a method, the fact that this condition or procedure worked in an unexpected and fruitful manner in the method supports the conclusion that the method was non-obvious. *See id.*

In the instant case, at least three reasons require a conclusion that the invention was non-obvious at the time of filing. First, the prior art teaches away from the instant invention. Second, one of ordinary skill in the art had no good reason nor suggestion to pursue the combination of prior art reference teachings suggested by the Office. And third, one of ordinary skill in the art had no reasonable expectation of success in arriving at the claimed invention.

1. The prior art teaches away from the instant invention

Rovati et al. (U.S. Patent No. 3,697,652) ("*Rovati*") teach pharmaceutical preparations, including injectable aqueous solutions, that contain as the active ingredient one or more acetylated amino sugars, such as, for example, N-acetylglucosamine (NAG):

> The pharmaceutical preparations according to the invention are characterized in that they contain as the active ingredient one or more N-acyl compounds of aminocarbohydrates. [...] The pharmaceutical preparations according to the present invention preferably contain N-acyl compounds of hexosamines and, more particularly of glucosamines and/or galactosamines. [...] The pharmaceutical preparations according to the invention can be administered orally, rectally or parenterally. It is preferred to administer them in the form of injectable aqueous solutions [...]. *Rovati*, col.1, lines 5-52.

Rovati further teaches that the acetylated amino sugars in solution can be heat-sterilized without difficulty, because they are "exceedingly stable" and do not decompose under the conditions described therein, which include higher-than-neutral pH:

> [I]t was found that the N-acyl compounds of aminocarbohydrates in aqueous solution remain stable even after sterilization [...].

Rovati, col. 1, lines 51-53.

> [T]he N-acetyl compounds according to the present invention are exceedingly stable. They can be sterilized without difficulty by heating in an autoclave.

Rovati, col. 3, lines 5-8.

Regarding the pH, *Rovati* teaches that heat sterilization of a solution comprising acetylated amino sugar(s), such as NAG, should be performed at a pH of 8.2-8.3. *Rovati*, col. 4, Example 5, lines 3-16.

Finally, *Rovati* advises against using different pH values during the preparation of the medical solution, because changing the pH was found to be detrimental:

> The essential advantage of the N-acetyl compounds according to the present invention over the corresponding salts, is the fact that they can be stabilized in a safer and better manner, without the necessity for a correction of the pH-value which was found to have a detrimental effect. *Rovati*, col. 3, lines 8-13 (emphasis added).

In summary, *Rovati* teaches that acetylated amino sugars can be heat sterilized in solution at a recommended pH of 8.2-8.3 and warns against changing the pH of the solution because it was found to have a detrimental effect.

According to the Federal Circuit, "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, . . . would be led in a direction

divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (emphasis added). Here, a person of ordinary skill, upon reading *Rovati*, would undoubtedly be led in a direction divergent from the path taken by the Applicants, in that the person of ordinary skill would be led to heat sterilize acetylated amino sugars at a pH of 8.2-8.3. Thus, *Rovati* teaches away from the instant invention.

A prior art reference that teaches away from the claimed invention and proceeding contrary to accepted knowledge in the art are evidence of non-obviousness. M.P.E.P § 2145(X)(D). That *Rovati* demands a conclusion of non-obviousness is further supported by the Supreme Court's holding in *United States* v. *Adams,* 383 U.S. 39 (1966) that an invention combining several elements known in the prior art was not obvious because the prior art teaches away from combining these elements:

> "Despite the fact that each of the elements of the Adams battery was well known in the prior art, to combine them as did Adams required that a person reasonably skilled in the prior art must ignore" the teaching away of the prior art that such batteries were impractical and that water-activated batteries were successful only when combined with electrolytes detrimental to the use of magnesium electrodes. *Id.* at 50–52 (emphasis added).

In the instant case, *Rovati* teaches that changing the pH during the preparation of medical solutions comprising amino sugars is detrimental. Applicants therefore respectfully submit that in view of *Rovati*'s teaching away, one of ordinary skill in the art would not have combined *Jonsson* and *Breborowicz* as proposed by the Office, which shows that the instant invention is not obvious over the cited references.

Moreover, at the time of the invention, nothing was known in the art about the degradation pathway of amino sugars, such as NAG. Applicants found that "the decomposition pattern for an amino sugar solution during heat sterilisation follows

specific Maillard reactions giving several different toxic decomposition products." Specification as-filed at page 9, ll. 22-35. Maillard reactions do not take place during heat sterilization of glucose-containing solutions. *Id.*, *see also* Figures 4a to 4d. As a result, many more and different decomposition products arise in case of amino sugar-containing solutions. *Id.* None of the known glucose degradation products were found in heat sterilized NAG solutions. *Id.* at page 3, line 36 - page 4, line 1. Based in part on these findings, Applicants were able to design a successful method for heat-sterilizing amino sugar solutions, which uses a low pH of 2.5-3.5 and is contrary to the teachings in *Rovati*. Since *Rovati* warns against using pH changes during the preparation of medical solutions containing amino sugars, the fact that the low pH during heat sterilization worked in the claimed method supports the conclusion that the method was non-obvious. *See KSR* at 1739-1741.

2. One of ordinary skill in the art had "no good reason" nor guidance to pursue the proposed combination of prior art references

One of ordinary skill in the art had no good reason nor guidance to pursue the proposed combination suggested by the Office for several reasons. First, *Rovati* teaches away from replacing glucose in *Jonsson*'s method of preparing a medical solution with the NAG of *Breborowicz*. *Jonsson* uses a low pH during heat sterilization of its glucose-containing solution, preferably a pH of about 3.5, and then changes the pH of the solution to neutral, i.e. to a pH of about 7.0:

> Suitably, the contents of the smaller glucose-containing package are maintained at a low pH during sterilisation, preferably in the order of 3.5. At the same time, the contents of the two packages during sterilisation should be maintained with such respective pH-values that the final resultant product after mixing is substantially neutral, i.e. with

> a pH between, for example, 6.5 and 7.5, preferably about 7.0.

Jonsson, col. 2, lines 51-57.

As discussed above, *Rovati* advises against using a pH different from the recommended pH of 8.2-8.3 because such change in pH can have detrimental effects.

Second, *Breborowicz* uses filtration, rather than heat, and a neutral pH, rather than a low pH, to sterilize its NAG-containing solution. *Breborowicz* at page S365, last full ¶ ("Fluids were sterilized by filtration and their pH was 7.05"). Furthermore, *Breborowicz* teaches that glucose and NAG are different compounds in the context of dialysis fluids, for example, causing different biological responses:

> During the subsequent days of experimental infusion with NAG-based dialysis fluid, a gradual decrease in the intraperitoneal inflammatory reaction was seen. No such effect was observed in animals exposed to glucose solution (Table 1). *Breborowicz* at page S367, 1st ¶.

Thus, one of skill in the art reading *Breborowicz* would have had no good reason to conclude that NAG and glucose are interchangeable compounds in the medical solution according to *Jonsson* in the context of heat-sterilization.

Third, *Jonsson* discloses using a low pH during sterilization specifically for glucose, but not for any other chemical compound that may replace glucose in the medical solution:

> Suitably, the contents of the smaller glucose-containing package are maintained at a low pH during sterilisation, preferably in the order of 3.5. *Jonsson*, col. 2, lines 51-53 (emphasis added).

> The small bag B can contain glucose concentrate, for example 20-500 ml, preferably 65-75 ml, 10-70% glucose, preferably 40%. The pH-value should lie between 3 and 6,

> preferably about 3.5. *Jonsson*, col. 4, lines 54-57 (emphasis added).

One of skill in the art would have had no good reason to conclude that the low pH used by *Jonsson* during sterilization of a glucose-containing solution would be applicable to the sterilization of a solution containing any other chemical compound, such as NAG, particularly given the disclosure in *Rovati* advising against changing the pH of the solution.

Lastly, both *Jonsson* and *Breborowicz* teach that the final pH of their dialysis solutions is neutral, i.e. a pH of about 7. *Jonsson*, col. 2, lines 51-57 ("[T]he final resultant product after mixing is substantially neutral, i.e. with a pH between, for example, 6.5 and 7.5, preferably about 7.0."); *Breborowicz* at page S365, last full ¶ ("Fluids were sterilized by filtration and their pH was 7.05"). Thus, one of skill in the art reading *Jonsson*, *Breborowicz*, and *Rovati* would have no suggestion to conclude that a solution containing NAG should be sterilized at a low pH of 2.5-3.5, as required by the claims, especially considering *Rovati*'s teaching that NAG can be heat sterilized without difficulty at a pH of 8.2-8.3, and that changing the pH was found to have a detrimental effect.

In summary, one of ordinary skill considering the art as a whole would have had no good reason or suggestion to combine *Jonsson* and *Breborowicz* to arrive at the instant invention.

Furthermore, according to the Supreme Court, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, at 1740-1741. Thus, merely by pointing

out that some of the elements of the instant invention were independently disclosed by *Jonsson* and *Breborowicz*, the Office has not made a *prima facie* case of obviousness.

3. There was no reasonable expectation of success in arriving at the claimed invention

One of ordinary skill in the art had no reasonable expectation of success in arriving at the claimed invention based on *Jonsson* and *Breborowicz* for the reasons presented in the amendment filed on July 13, 2009, and the additional arguments discussed in the previous sections,

As mentioned in Section A, the melting point alone does not provide information relevant to the stability of a compound under the conditions recited in the instant claims.

Furthermore, *Jonsson* is silent on terminal sterilization of acetylated or deacetylated amino sugar solutions, disclosing only heat-sterilization of glucose solutions. *Jonsson*'s glucose compounds differ in their chemical properties from amino sugars. Amino sugars contain an "amino group and possibly an acetyl group coupled to the glucose ring." Specification at page 4, lines 4-7. Because of this additional amino group, and possibly acetyl group, amino sugars can participate in chemical reactions different from those in which glucose can participate, and at least some of these reactions are influenced by temperature. This is demonstrated, for example, in the instant specification by the comparison of the degradation patterns of heat-sterilized NAG and glucose solutions. The specification discloses that, in contrast to glucose, "none of the known glucose degradation products has been found in heat sterilised NAG solutions." Furthermore, the specification discloses that "the decomposition pattern for an amino sugar solution during heat sterilisation follows specific Maillard reactions giving several different toxic decomposition products." Specification at page

9, lines 22-35. Maillard reactions *do not* take place when only glucose compounds are present in solution. *Id.*, *see also* Figures 4a to 4d, which compare the decomposition patterns of glucose-containing solutions with amino sugar-containing solutions. The number of decomposition products is much larger in the case of amino sugar-containing solutions due to the Maillard reactions.

Knowledge of the degradation pathway for an organic compound is relevant for determining suitable conditions for sterilizing a solution comprising the compound. The degradation pathway for amino sugars, such as NAG, however, was not known prior to the present invention:

> [N]one of the known glucose degradation products has been found in heat sterilised NAG solutions. This fact has not been known previously and forms the basis for the present invention.

Specification at page 3, lines 337, to page 4, line 3. Without such knowledge, one of ordinary skill in the art would have had no reasonable basis to expect that the conditions disclosed in *Jonsson* for the heat-sterilization of glucose solutions could be successfully applied to the heat-sterilization of amino sugar solutions.

Breborowicz did nothing to change this lack of reasonable expectation of success. *Breborowicz* sterilized the acetylated amino sugar NAG by filtration, not by heat, and used a neutral pH, not the low pH of *Jonsson*.

The lack of reasonable expectation of success was compounded by *Rovati*'s teaching away from using a low pH for amino sugars due to detrimental effects.

Accordingly, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, because one skilled in the art would not have had a reasonable expectation of success based on *Jonsson* and *Breborowicz*.

In summary, Applicants respectfully submit that claims 1, 3-11 and 17-25 are not obvious over *Jonsson* and *Breborowicz* for at least the independent reasons outlined in sections A and B above. Thus, Applicants request that the rejections under 35 U.S.C. §103(a) be withdrawn.

IV. Conclusion

Applicants therefore request reconsideration of the application in view of the above remarks, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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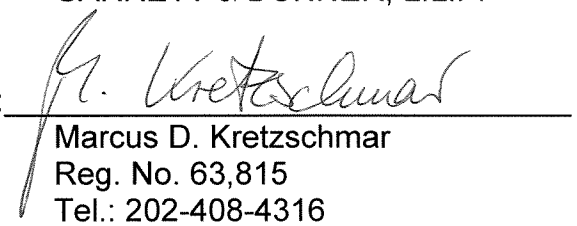
By: 

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